Canadian Agency for Drugs and Technologies in Health

RAPID RESPONSE REPORT:
SUMMARY WITH CRITICAL APPRAISAL

TITLE: Obesity Interventions Delivered in Primary Care for Patients with Diabetes: A Review of Clinical Effectiveness

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CONTEXT AND POLICY ISSUES

Type 2 diabetes is characterized by high blood glucose and is often associated with several metabolic abnormalities. Excess body weight, particularly visceral adiposity, may contribute to the development of both diabetes and the associated metabolic abnormalities.[1] When the energy consumed through foods is not balanced by energy expended through physical activity, unused calories are stored in the body as fat (adipose tissue), which can accumulate in excess and results in overweight and obesity.[2] Adipose tissue is an active endocrine and immune organ whose dysfunction contributes to metabolic diseases including diabetes and increases cardiovascular disease.[3] Thus, the benefits of weight loss in overweight/obese patients with type 2 diabetes extends beyond cosmetic to include improvement in the health of patients in terms of enhanced glycemic control and mobility, and a decreased need for some medications.[3,4]

Increase in body weight is a common side effect of many antidiabetic medications.[3,5] One implication for this untoward effect is that implementing lifestyle intervention in overweight/obese type 2 diabetes patients could be challenging because their higher than normal body weight may require an increase in antidiabetic medication to achieve desired glycemic control, and many find it difficult to modify lifestyle sufficiently and long enough to reduce weight, thus creating a vicious cycle.[3,5]

Treatments for obesity either decrease energy intake or increase energy expenditure.[6] Strategies for weight loss in obese patients with type 2 diabetes include lifestyle and pharmacological interventions. Dietary adjustment is a critical component of lifestyle intervention and usually includes low-carbohydrate and low-fat diets, though decreased caloric consumption is necessary irrespective of the sources.[7-9] Increased energy expenditure through a stepped-up physical activity program and behavior modification to correct imbalance in caloric intake are also essential to lifestyle intervention.[7-9] Though many drug interventions for overweight/obesity are available, several of them have not been approved for long-term use, and several may be contraindicated in obese diabetes patients due to co-morbidities and/or risk of complications.

Setting realistic weight loss goals is important in weight loss programs to achieve beneficial target. Goals that are too high or too low may result in program failure because unattainable goals may be a disincentive to patients, while weight reduction below a modest threshold may not have much health benefit. A weight loss goal of 5 to 7% of body weight has been described as realistic for most individuals to begin with.[3,6,7] Weight loss of 7% has been to reported reduce the rate of progression from impaired glucose tolerance to diabetes by 58% in a study population.[9]

A Statistics Canada report[10] indicates that reported cases of diabetes among Canadians aged 12 years or older increased from 5.8% in 2007 to 6.5% in 2012; and in 2012, 14.7% of obese Canadians 18 years or older had diabetes compared with 5.1% of those who were not obese. In view of the potential health and wellness benefit of weight loss to obese diabetic patients, this report aims to provide current evidence on the clinical effectiveness of various obesity management interventions that could be used in primary care settings to halt or slow the progression of type 2 diabetes.

RESEARCH QUESTION

What is the clinical effectiveness of long-term primary care obesity management interventions in halting or slowing the progression of type 2 diabetes?

KEY FINDINGS

In using a lifestyle approach to achieve weight loss in overweight or obese patients with type 2 diabetes, it has been shown that decreasing caloric intake produced greater weight loss than physical activity in the short-term (6 months); however, a combination of diet and exercise were needed to achieve and maintain weight loss in the long-term (≥12 months). Significantly greater proportions of patients using pharmacological interventions achieved reductions of 5% or more of their initial weight compared to those receiving a standardized lifestyle intervention. Weight loss in overweight/obese type 2 diabetes patients was associated with better glycemic control (as demonstrated by improved insulin sensitivity, fasting blood glucose, and HbA1c), improved quality of life, and reduced risk of loss of mobility. Satisfactory weight reductions were achieved when energy expenditure was increased to 1000 kcal/day and beyond, and improvements in glucose control appeared to be associated with weight loss of 5% or more. Improvements in blood glucose control resulted in reduction (in some cases discontinuation) of antidiabetic medication usage for some patients. Despite challenges faced by some obese patients with type 2 diabetes to reach the threshold weight loss (≥ 5% initial body weight) required to realize clinically meaningful glycemic control, continued efforts have been encouraged given that modest intentional weight loss can improve cardiovascular risk factors and decrease mortality.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including Medline, PsycINFO, PubMed, The Cochrane Library (2014, Issue 5), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials and non-randomized studies. Where possible, retrieval was limited to the human

population. The search was also limited to English language documents published between January 1, 2009 and May 27, 2014.

Selection Criteria and Methods

One researcher screened the citations and abstracts from the literature search and selected articles according to the selection criteria outlined in Table 1, and a second researcher examined the full-text publications for the final study inclusion for this report.

Table 1: Selection Criteria

Population	Adults with body-mass-index (BMI) of 30 or higher who have type 2 diabetes
Intervention	Non-surgical interventions for weight management that can be delivered in primary care or community care, including one or more of the following interventions: pharmacological, lifestyle (diet/healthy eating, exercise), or psychological therapy, applied for a duration of six months or longer
Comparator	Care that is not specialized for obesity/weight management
Outcomes	Diabetes status (+/-), medication burden (number and reliance on medication), organ damage (retinal, renal); limb compromise (diabetes ulcers, amputations); glycemic control; mental health/illness – quality of life (QoL); depression severity index scores
Study Designs	Health Technology Assessments (HTA)/Systematic reviews/Meta-analyses; Randomized controlled trials (RCTs), and Non-randomized studies.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria in Table 1. In particular, studies that focused on surgical interventions, and interventions targeting diabetes alone (e.g. antidiabetic drugs) or change in BMI alone were not included. Studies were also excluded if they were published before 2009, if they did not have a comparator group, if they were duplicate publications of an already selected study, or if they were of insufficient methodological quality or lacked reporting detail required to permit appropriate analysis and interpretation.

Critical Appraisal of Individual Studies

The quality of studies included in this report was appraised using the SIGN-50 Methodology Checklist 2 for controlled trials.[11] The strengths and limitations of the individual studies have been summarized and presented in tabular form in Appendix 3.

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search yielded 461 citations of which 25 potentially relevant studies were selected upon screening of titles and abstracts. Grey literature searching identified an additional 10 papers bringing the total pool of potential articles to 35, of which five unique studies were selected for inclusion in this report. In addition, findings from five additional articles in which investigators conducted secondary analyses to highlight and provide details of different specific outcomes associated with weight loss in one of the selected studies (the Look AHEAD trial)[12] have been included. The objectives and findings of the latter five articles have been

summarized in Appendix 5. All the included studies were randomized controlled trials. The PRISMA flow chart in Appendix 1 outlines the selection process.

Summary of Study Characteristics

Characteristics of included studies have been summarized in Appendix 2.

Country of origin

Four of the unique studies[3,4,7,12] are from the United States of America (USA). The remaining is from Germany.[8] One of the studies from the USA, the Look AHEAD trial,[12] was the source of data for the five other articles included in this report, with finding summarized in Appendix 5

Study setting

The Look AHEAD trial[12] was conducted in sixteen clinical sites in the USA. Another study, (BLOOM-DM)[7] was conducted at 58 academic and private research sites in the USA. A third study (by the COR-Diabetes Study Group)[3] from the USA only states that the trial was conducted at 53 sites without exact description of the settings. A fourth trial from the USA was a single center study[4] conducted in a medical center at a University Hospital. The study from Germany[8] was conducted at a University Hospital. Participants in all the included studies were out-patients.

Patient population

Participants in all the studies were overweight/obese, adult (18 years or older) type 2 diabetes patients. The inclusion criteria of all the studies required patients to have body mass index (BMI) of 25 kg/m^2 or more, and the mean BMI exceeded 30 kg/m^2 for each study. Participants were also required to have elevated plasma glucose and/or glycated hemoglobin (HbA1c). In both of the pharmacological studies,[3,7] participants had HbA1c between 7% and 10%. The mean baseline Hb1Ac was identical (8.1 ± 0.8%) for all study arms in one study,[7] and well balanced across study arms for the other study.[3] One of studies[8] of lifestyle interventions reported mean baseline HbA1c of 7.5% ± 1.1% for the intervention group and 7.6% ± 1.1% for the control group. No cut-offs for inclusion were reported. For another study,[4] the mean baseline HbA1c was 7.5% ± 1.5% for one arm and 7.4% ± 1.4% for the other. The Look AHEAD trial[12] reported an overall mean HbA1C of 7.25 ± 1.1%. Two studies[4,12] reported an upper limit HbA1c cut-off of 11% for enrolled participants.

The majority of participants were female for all the studies. Women formed nearly 56% in one of the pharmacological studies[3] and 54% in the other.[7] One of studies[8] of lifestyle interventions had 51.5%, and another study[4] had 78.1% female. In the Look AHEAD study[12] 59% of participants were women. For studies that provided information about participant ethnicity, the Look AHEAD and the BLOOM-DM trails[7,12] had a majority of white participants, while the majority or participants in the two other studies[3,4] was black. The Look AHEAD study[12] enrolled only participants aged 45 to 76 years while the other two lifestyle intervention studies did not set upper limits of age as inclusion criteria. The BLOOM-DM study[7] restricted the upper limit of participants' age to 65 years and the other pharmacological study had 70 years as the upper limit. In one study,[3] participants were excluded if they were using insulin or antidiabetic medication from the glucagon-like peptide-1 class. The BLOOM-DM study[7] enrolled only

patients on treatment with either metformin, a sulfonylurea (SFU), or both. Patients on other antidiabetic medications were excluded.

Interventions and comparators

Two studies,[3,7] evaluated pharmacological interventions for weight loss while three others[4,8,12] investigated lifestyle interventions for weight loss.

Pharmacological Interventions

The BLOOM-DM study[7] randomized 604 participants in a 1:1:1 ratio to placebo, lorcaserin 10 mg once daily (QD) or lorcaserin 10 mg twice daily (BID) for a 1 year (52 week) study. Only metformin or an antidiabetic medication from the sulfonylurea class was allowed as background therapy. Medication use was well balanced across study arms with most participants in each arm (91% to 95%) treated with metformin, nearly 50% receiving sulfonylurea, and between 41% and 47% treated with both metformin and sulfonylurea.

In the second pharmacological intervention study,[3] 505 patients were randomized to receive a daily dose of 32 mg naltrexone and 360 mg bupropion (NB) in fixed-dose combination (FDC) or placebo for a 56-week trial which included a 4-week initial period when the dose was titrated to the maximum. Both components of the FDC were sustained release preparations. Participation in this study[3] was allowed if patients had been on stable doses of oral antidiabetic medication for at least 3 months prior to randomization, or not taking a diabetes medication. However, patients were not allowed if they used insulin or antidiabetic medication from the glucagon-like peptide-1 class.

Participants in both arms of each of the two pharmacological intervention studies[3,7] received standardized lifestyle modification interventions.

Lifestyle Interventions

Lifestyle interventions employ diet/healthy eating, exercise, or behavioral changes to achieve weight loss.

In the Look AHEAD trial,[12] 5,145 participants were randomized to an intensive behavioral intervention referred to as Intensive Lifestyle Intervention (ILI) or standard diabetes support education (DSE). The Look AHEAD trial was a 4-year study, with follow-up visits past Year 4 intended primarily for collection of data on cardiovascular disease (CVD) events and those measures that potentially mediate the effect of the intervention on CVD events (weight, blood pressure, lipids, and HbA1c). All participants continued on medical care provided by their personal physicians, including changes in medication, except temporary adjustment to avoid hypoglycemia during periods of intensive weight loss for patients in the ILI arm.[12]

Specific components of the ILI included daily caloric goal of between 1200 and 1800 calories depending on initial body weight, and a home-based exercise plan involving 175 minutes or more per week of physical activities similar in intensity to brisk walking. The caloric intake plan required less than 30% of total calories from fat (with less than 10% from saturated fat), and a minimum of 15% of total calories from protein. Participants were provided with pedometers to motivate them and they could count any moderate activity toward the exercise goal provided it was at least 10 minutes in duration and of similar intensity to brisk walking.[12]

Furthermore, patients in the ILI group were seen weekly for the first 6 months, and three times per month for the next 6 months either individually or in a group. Subsequently, they were seen individually at least once a month, contacted by phone or email once a month, and given the opportunity to participate in a variety of approved group classes.[12]
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Participants in the DSE group used standardized protocols focused on diet, physical activities and social support. Though they were offered three group sessions per year, information on behavioral strategies was not provided and patients were not weighed.[12]

In a second study,[4] 105 participants were randomized to receive either a low-carbohydrate or a low-fat diet over a 12 month period. The low-carbohydrate diet was initiated with a 2-week phase of carbohydrate restriction of 20 to 25 grams daily, and carbohydrate intake was increased at 5 gram increments each week if weight loss was achieved.[4] In the low-fat diet group, participants were given a fat gram goal that was 25% of energy needed to achieve a 1- to 2-pound weight loss per week based on their baseline weight.[4]

In a third study,[8] 70 participants were randomized 1:1 to either the Active Body Control (ABC) program or standard therapy for a 6-month study. Key components of the ABC program are diet which avoids calorie-rich foods and emphasized preference for carbohydrates of low glycemic index (but not avoidance of carbohydrates), telemonitoring of participants' weight and physical activity, and a weekly feedback letter from investigators to inform and motivate the patient.[8] Standard therapy comprised the conventional low-fat diet and standard care according to recommendations issued by the Deutschen Diabetes-Gesellschaft.[8]

Outcome Measures

Pharmacological intervention studies

The primary outcome of the BLOOM-DM study[7] study was weight loss. Secondary outcomes included glycemic control, changes in BMI (weight in kg/height in m^2) from baseline, and quality of life. Glycemic control was evaluated using HbA1c, fasting glucose, and calculated insulin resistance. Quality of life was assessed by the Impact of Weight on Quality of Life-LITE questionnaire (IWQOL-LITE). Patients were monitored for possible depression using the Beck Depression Inventory-II (BDI-II) score.

In the second pharmacological intervention study,[3] percent weight change and achievement of 5% or more initial weight loss were co-primary end points. Secondary end points included achievement of HbA1c less than 7%, achievement of weight loss 10% or more, and change in HbA1c, and fasting blood glucose.

Lifestyle intervention studies

The major outcomes examined by the Look AHEAD study[12] were changes weight, physical fitness, and cardiovascular risk factors. Weight and height were measured in duplicate using digital scale and stadiometer. A submaximal exercise test was given at Years 1 and 4 (and for a subset of participants at Year 2) following a maximal graded exercise test at baseline. Cardiovascular risk factors were evaluated through changes in blood pressure and lipid parameters from baseline, using automated device and standardized laboratory procedures, respectively. In addition, HbA1c was assessed using standardized laboratory procedures, and

participants' health related quality of life (HRQOL) status was measured using the SF-36 instrument. Cardiovascular risk outcomes are not presented or discussed in this report.

Another lifestyle intervention study[4] used the Diabetes-39 instrument (a 39-item questionnaire) to assesses five distinct aspects of diabetes-related quality of life (QOL): anxiety and worry (4 items), diabetes control (12 items), energy and mobility (15 items), social burden (5 items), and sexual functioning (3 items). The Diabetes-39 is a self-administered tool which has been validated among patients with type 1 and type 2 diabetes with results well correlated to the SF-36 instrument used to measure health-related quality of life (HRQOL).[4]

In a third lifestyle study,[8] the primary outcome was weight loss while the metabolic and cardiovascular risk markers (glycemic control, blood pressure, and lipid parameters), and antidiabetic drug usage were secondary endpoints.

Summary of Critical Appraisal

Appendix 3 provides further details of the critical appraisal of individual studies.

Pharmacological interventions studies

The two trials[3,7] involving pharmacological weight loss interventions were double-blind randomized controlled studies. However details of randomization and concealment were not provided for either of them. In both studies,[3,7] baseline characteristic of participants were well-balanced and primary efficacy analyses were performed using the modified intent-to-treat (mITT) population with last observation carried forward for missing data. The mITT population is defined as randomized participants with a baseline and at least one post-baseline measurements of body weight while on the study drug.

Both studies[3,7] had sample sizes large enough to provide power to determine relevant clinical differences in weight loss between treatment groups. There was no information in either study to suggest that it was powered to detect differences in non-weight loss outcomes, however it is likely, based on the sample size and power, that the studies were adequate to detect differences in these secondary outcomes. Each of the two studies[3,7] measured pre-specified outcomes with reliable tools and provided well done reports with rigorous statistical analysis. Though each of the trials[3,7] was multi-centered, they each presented a composite result for all sites and comparability of outcomes from individual sites could not be determined for either of them. The dropout rate was high in both studies.[3,7]

In one trial,[3] more participants in the placebo group completed the study compared with those on the study drug (58.8% versus 52.2%, respectively). The most common adverse event (42%) reported with the study drug (NB) was nausea, accounting for 9.6% of patients who withdrew from the NB arm. Nausea occurred at a greater incidence in NB treated patients taking metformin at baseline (46.2%) compared with those not on metformin (28.2%).[3]

In the other trial,[7] more patients assigned to lorcaserin BID (66.0%) and lorcaserin QD (78.9%) completed the study as compared to placebo (62.1%). More discontinuations were attributed to adverse events in the lorcaserin BID (8.6%) and QD (6.3%) groups than in the placebo group (4.3%). The most common adverse events with greater incidence in the lorcaserin group than placebo were headache, back pain, nasopharyngitis, and nausea. Withdrawal of consent was the most frequent reason for early discontinuation in all treatment groups.

Investigators of each of the studies stated that high dropout rates are characteristic of studies in obesity drug development and the proportion of dropouts from their studies did not differ from other reported studies. However, these high dropout rates should be considered when evaluating the treatment effect of the two studies.[3,7] Generally, each of the studies in the pharmacological obesity intervention was well conducted without major concerns for potential biases.

The participants in the two studies were predominantly white with the majority being female. This is likely generalizable to the population of obese diabetic patients in Canada. The Public Health Agency of Canada (PHAC) reports that among females aged 18 years and older, the prevalence of diabetes among overweight or obese individuals is nearly four times higher than those who are of normal weight (9.6% versus 2.6%), while among males aged 18 years and older the prevalence is 2.6 times higher among overweight or obese individuals than among those with normal weight (9.7% versus 3.8%).[2] The prevalence of obesity in Canada is 19.7% in Caucasians compared with 18.7% and 9.5% in people of African and South Asian descent, respectively.[2] However, according to PHAC, people of South Asian, Hispanic American, Chinese, and African ancestry are at higher risk of developing type 2 diabetes than those of European descent owing to both biological and behavioral differences that influence diabetes risk.[2] Specific race/ethnicity-based data on diabetes prevalence/incidence in Canada were not provided, therefore it is unclear whether the participants of the included studies were generalizable to the Canadian population in that regard.

The BLOOM-DM study[7] restricted participation to patients who were taking either metformin or sulfonylurea, while the other pharmacological study[3] excluded patients who were on insulin or glucagon-like peptide-1 agonist antidiabetic drugs. The extent to which there measures would affect the applicability of findings of these studies to the other obese diabetic population is uncertain.

Lifestyle intervention studies

All the three studies[4,8,12] which investigated lifestyle interventions in overweight/obese type 2 diabetes patients were randomized controlled trials. However, their nature makes concealment and blinding impractical to implement. Baseline characteristics of participants were well-balanced across treatment groups in all the studies and all relevant outcomes were measured in a standard, valid, and reliable way.[4,8,12]

The Look AHEAD study,[12] had a large sample size (n=5,145) and it is the longest, continuously implemented lifestyle intervention for weight management to date (2014).[12] It is reported to have >80% probability of detecting an 18% difference in major cardiovascular disease events between the two study groups. The remaining two studies[4,8] were also powered to detect relevant differences in weight between treatment groups. Neither of the two studies[4,8] indicated that it was powered to detect differences in non-weight loss outcomes.

For all the three studies,[4,8,12] analyses were performed using intention-to-treat (ITT) population with outcomes for participants treated according to the group to which they were originally randomized regardless of the number of treatment visits they attended. The Look AHEAD[12] study does not provide information about how missing data were handled. In one study,[4] missing data were handled in two ways. If questionnaires were missing more than 4 items (excluding values from Sexual Functioning Scale) they were excluded from the analysis and mean scores for each scale were imputed for missing values. Secondly, missing 12 month QOL

data were imputed using 6-month data. The investigators reported that analysis with and without imputation of missing 12 month data showed no difference in the results. In another study[8] last observation carried forward (LOCF) was applied. It must be noted that in this study[8] only two participants (both in the control group) dropped out, and it is not expected to affect the reported outcome in a significant way.

All the three lifestyle intervention studies[4,8,12] had high retention rates. One study[4] had 82% overall retention. However, despite the high proportion of participants who completed this study,[4] approximately half of them did not complete the Diabetes-39 questionnaire used to evaluate quality of life. A second study[8] reported a 100% retention in the control group and 94% in the intervention group, while the Look AHEAD trial[12] reported that 94.1% of participants in the intervention arm (ILI) and 93.1% in the comparator arm (DSE) completed the 4-year assessment.[12]

For all the participants in the Look AHEAD trial, assessment of weight and many other outcomes were conducted yearly after baseline measurements.[12] The interval between measurements may be long and potentially important variability in outcome trends could be missed. Also, an important reference for physical activity (brisk walking) was not scientifically defined so that its interpretation can be subjective and difficult to determine if reproducibility has been attained. Overall, all the three lifestyle intervention studies for obese type 2 diabetes patients were well done, however, absence of blinding and the use of self-reported data, as well in all the studies, as well as failure of nearly one half of participants in one study[4] to complete questionnaire to assess an important outcome must be considered when interpreting the finding..

In the Look AHEAD trial,[12] a key source of generalizability concerns for a primary care setting is that participants of the study were provided with two free meal replacements per day for the first 4 months and then one free meal replacement per day from the 5th to the 12th months.[12] These may have improved adherence to the program and contributed in part to the observed positive outcomes. It is uncertain how the absence of free meal replacements in primary care settings may lead to different results from the study findings. Furthermore, since the Look AHEAD trial excluded patients who were younger than 45 years or older than 76 years, the generalizability of the study findings to obese type 2 diabetes patients outside the included age population brackets of is indeterminate.

The two other studies[4,8] were conducted at settings (academic medical center and university Hospital) that are significantly different from primary care facilities in terms of staff and technology employed in the studies. In addition, exclusion criteria in one study[4] included kidney or heart disease (which could reasonably be expected to be common among obese type 2 diabetes patients); and the other study[8] used technology (telemonitoring) that may be too costly to acquire and implement in a primary care setting, though the investigators stated that their analysis shows the ABC intervention was comparable in cost to other treatment options in Germany where the study was conducted. Owing to these issues, generalizability of results from these studies to primary care settings is uncertain.

Summary of Findings

Evidence for the research question is presented in the following paragraphs. Further details on individual study findings and authors' conclusions have been provided in Appendix 4**.**

Pharmacological interventions

One pharmacological obesity intervention study[7] reported that patients treated with lorcaserin 10 mg once daily (QD) or twice daily (BID) in addition to diet and exercise counselling achieved greater reduction in weight than those who received diet and exercise counselling alone. The proportion of patients who lost ≥5% body weight with lorcaserin was greater regardless of whether it was dosed QD (44.7%; P < 0.001) or BID (37.5%; P < 0.001) compared with placebo (16.1%).

Statistically significantly greater proportion of patients treated with lorcaserin achieved HbA1c ≤7% at week 52; with 52.2% of patients in lorcaserin 10 QD group and 50.4% in the lorcaserin BID group compared with 26.3% in the placebo group. Participants who received lorcaserin also demonstrated greater improvements in fasting glucose and insulin resistance than those in the placebo group.[7]

More patients taking lorcaserin decreased the overall use of oral antidiabetic medications, but this result was not statistically significant (23.4%, 17.1%, and 11.7% in the lorcaserin QD, lorcaserin BID, and placebo groups, respectively; P = 0.087), and fewer patients taking lorcaserin increased the total daily dose of antidiabetic agents (11.7%, 13.5%, and 22.2%, respectively; P = 0.011).[7] Quality of health as determined by the IWQOL-LITE questionnaire score improved in all treatment groups with greater but not statistically significant different improvements occurring in patient who received lorcaserin.[7]

Another study[3] found that FDC drug (NB) with a daily dose of 32 mg naltrexone and 360 mg bupropion (sustained release formulation of each) resulted in significantly greater weight reduction than placebo (-5.0% vs. -1.8%; P < 0.001). A statistically significantly greater proportion of patients on NB achieving ≥5% weight loss (44.5% vs. 18.9%, P < 0.001) compared with placebo.[3] The drug also resulted in significantly greater HbA1c reduction than placebo (-0.6 vs. -0.1%; P < 0.001), and a significantly greater proportion of patients treated with NB achieved clinically important HbA1c <7% than those who received placebo (44.1 vs. 26.3%; P < 0.001).[3]

Lifestyle interventions

The Look AHEAD trial[12] reported that participants in ILI had greater percent weight losses averaged across four years of follow-up, than those in DSE (−6.15% vs −0.88%, P < 0.0001). The ILI group also achieved significantly greater improvements in glycemic control than placebo as indicated by reduction in HbA1c (−0.36% vs. 0.09%, P < 0.0001); and their fitness improved more than patients in the DSE group (12.74% vs. 1.96%, P < 0.0001).

Another study[4] found that obese type 2 diabetes patients on either a low-carbohydrate diet or a low fat diet achieved a mean (± SD) weight loss at 12 months of 11 (±11) pounds. The participants also reported significant improvement in quality of life over baseline in the domains of sexual function, and energy and mobility (P = 0.01), and they experienced a trend toward improvement in anxiety and worry (P = 0.06). There was no significant difference between the 2 dietary arms with regards to these improvements (P = 0.58).

A third study[8] reported that reduction in baseline body weight in excess of 5%, 10%, and 15% occurred in 82%, 51% and 27% of patients treated with the ABC intervention for 6 months, respectively. There was reasonable correlation between daily average energy expenditure and weight loss, with r = -0.58 (P = 0.000).[8]

Patients who used ABC experienced a mean reduction of 10% (±5.9%) of baseline HbA1c, while the control group had their glycemic control deteriorated as indicated by an upward trend of HbA1c by 3% (P = 0.053).[8] The proportion of patients in the ABC group with HbA1c values above 7% decreased from 57% at baseline to 26% at 6 months. In contrast, the proportion of patients with HbA1c ≥7% in the control group increased from 74% at baseline to 80% at 6 months.

With improvements in glycemic control, patients in the ABC group, 14 patients (42%) reduced their antidiabetic medication compared with 3 (8%) in the control group. Thirteen patients (39%) in ABC compared with 3 (8%) in the control did not require antidiabetic medication at 6 months while more patients in the control group either had new prescriptions or increases the dose of their original antidiabetic medications.[8]

Further evidence from the Look AHEAD trial[12]

Findings from the five original articles which examined specific benefits of weight loss to obese diabetic patients using secondary analysis of data from the Look AHEAD trial have been summarized in this paragraph (see Appendix 5 for more details). One of the articles[13] reported that older participants (65 to 76 years) achieved greater weight loss and fitness than younger participants (45 to 64 years) at 4 years. A second article[14] showed that moderate weight loss using ILI was not associated with symptoms of depression and suicidal ideation; rather symptoms of depression was significantly lower in the ILI group compared with the DSE group (6.3% versus 9.6%) at 1 year. In addition, in all treatment groups, weight loss achieved in participants with baseline symptoms of depression was comparable to those without symptoms of depression at baseline. There were no clinically meaningful differences between them. Another article[1] reported that the relative reduction in the risk of loss of mobility was greater among patient in ILI compared to those in DSE (odds ratio [OR]=0.52; 95% confidence interval [CI]: 0.4 to 0.63; P < 0.001). A fourth article[15] found that severely obese (BMI ≥40 kg/m^2) type 2 diabetes patients on ILI achieved significantly greater weight loss compared to overweight patients (BMI 25 to <30kg/m^2) patient but comparable to Class I (BMI 30 to <35kg/m^2) and Class II (BMI 35 to <40kg/m^2) obese type 2 patients on the same treatment. Yet another study[16] reported that participants who achieved ≥10% weight loss at the end of year 1 and were able to maintain the loss through year 4 had significantly more treatment contacts with behavior counsellors per year between year 2 and year 4 than those individual who regained to their baseline weight.

Limitations

Limitations of included studies have been summarized in Appendix 3

Limitations of the report

This report has limitations that need to be considered when interpreting its findings. First, all the included studies were conducted outside Canada and it is uncertain how applicable their findings will be among obese type 2 diabetes patients in primary care settings in Canada. Furthermore, the two pharmacological studies[3,7] were evaluated based on single articles for each authored/sponsored by the manufacturers of the drugs being evaluated. A more rigorous appraisal of clinical trials may have relied on data from the complete clinical study reports (CSRs). Therefore, though this review did not find any major quality issues with the studies, it is

uncertain whether an exhaustive assessment of their internal validity was achieved given the paucity of information used for the evaluation.

Pharmacological intervention studies

Questions about the generalizability of findings from both studies[3,7] remain due to their exclusion criteria which denied participation to patients with characteristics common in the obese type 2 diabetes population. Furthermore, both studies[3,7] were conducted at research sites with staff and facilities that may be significantly different from a primary care setting, making it uncertain how generalizable the findings will be to the latter. One of the studies[3] used placebo as a comparator while the other[7] compared a drug to lifestyle intervention. This seems problematic because pharmacological intervention for weight loss is usually initiated upon inadequate response to lifestyle intervention, and placebo is not a practical treatment option.

Lifestyle intervention studies

In the Look AHEAD study[12] excluded participants who were younger than 45 years or older than 76 years. In addition participants were provided with meal replacements free of charge which may be too costly to replicate in a primary care setting. In a study[4] which evaluated quality of life (QOL) of participants (n=105) on different diets for 12 months, the retention was reasonable high at the end of the study but only 54 (51%) and 46 (44%) participants completed the Diabetes-39 assessment questionnaire for QOL at 6 and 12 months, respectively. Thus, the interpretation of findings from the study with regards to changes in QOL must be done with care.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

Weight loss in obese type 2 diabetes patients was achieved through either pharmacological interventions or lifestyle intervention, or both. A significantly greater proportion of patients who used pharmacological intervention achieved target weight loss goals than patients who received diet and exercise counseling. Patients who combined pharmacological interventions with standardized lifestyle interventions achieved a greater percentage weight loss than those who received standardized lifestyle intervention alone.[3,7] Intensive lifestyle intervention (ILI) as described in the Look AHEAD study[12] resulted in significantly greater proportion of patients losing weight than those who received diabetes support education (DSE) with patients in the ILI achieving greater percentage loss from baseline weight. Significant weight loss in obese type 2 diabetes patients was associated with improved glycemic control in all studies regardless of the choice of intervention, whether pharmacological or lifestyle. Other benefits demonstrated by study participants who lost significant weight included improvements in quality of life and reduction in the risk of losing mobility. Evidence from the Look AHEAD study[12,15] suggests that all classes of obese type 2 diabetic patients can benefit from lifestyle or pharmacologic intervention provided their individual condition is not a contraindication to the intervention. A higher proportion of obese type 2 diabetes patients who achieved a reduction of 5% or more of their initial body weight achieved significantly greater glycemic control and required less antidiabetic drugs than those who did not.[3,4,7,8,12]

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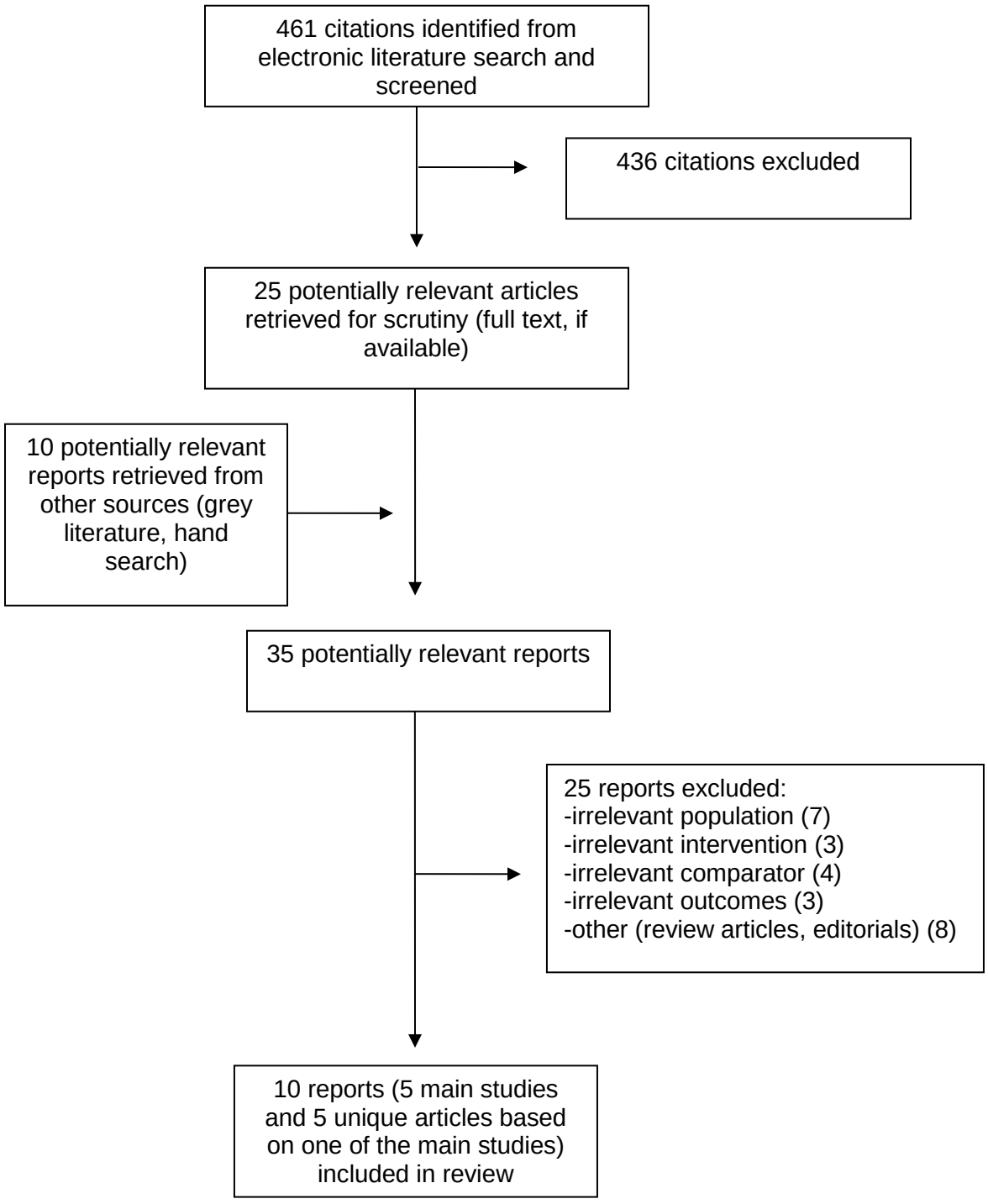
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Studies

First Author, Publication year, Country	Study Design	Patient Characteristics	Intervention	Comparator	Clinical Outcome*
The Look AHEAD Research Group,[12] 2010 USA	RCT	Overweight/obese type 2 DM patients with average (Mean ± SD), age and BMI of 58.7 ± 6.8 years and 36 ± 5.9 kg/m^2, respectively	ILI	DSE	Changes in Weight, physical fitness and cardiovascular risk
O'Neil,[7] 2012 USA	RCT	Adult (18 to 65 years old) type 2 DM patients (n=604) with HbA_1C of 7 to 10%) and had BMI of 27 to 45 kg/m^2	Lorcaserin 10 mg QD or BID	Placebo	Co-Primary endpoints: The proportion of patients who lost ≥5% baseline body weight; Mean body weight change; and the proportion of patients who lost ≥10%) Secondary: Changes from baseline in glycemic control (HbA_{1c}, fasting glucose, fasting insulin), BMI, and QOL.
Davis,[4] 2012 USA	RCT	Adult (≥18 years) obese type 2 DM patients (n=105)	Low-carbohydrate diet	Low-fat diet	Changes in diabetes-specific quality of life (QOL) using Diabetes-39 questionnaire, Mean loss in baseline body weight.
Luley,[8] 2011 Germany	RCT	Type 2 DM patients, with a mean age and BMI of nearly 58 years and 35 kg/m^2, respectively; elevated plasma glucose and/or HbA1c and/or regularly using antidiabetic medication. (n=70)	Active Body Control (ABC) Program	Standard therapy	Primary: weight loss Secondary: antidiabetic drug usage
Leader,[5] 2013 Australia	RCT	Obese type 2 diabetes patient (n=36)	1 meal PMR/day	2 meal PMR/day	Primary: Compliance and dropout rates Secondary: Weight, waist and HbA1c changes
Hollander,[3] 2013 USA	RCT	Overweight/Obese type 2 diabetes patients (n=505) with standardized lifestyle intervention, with or without background oral antidiabetic drugs. Mean age, BMI, and HbA1c were 54 yrs., 37 kg/m^2, and 8.0%, respectively.	Naltrexone sustained-release (SR)/ bupropion SR (NB)	Placebo	Primary: Percent weight change and achievement of ≥5% weight loss. Secondary: Achievement of HbA1c <7% and weight loss o ≥10% from baseline; and change in HbA1c, and fasting blood glucose.

BMI=body-mass index; ; **BID**=twice daily; **DB**=double-blind; **DM**=diabetes mellitus; **DSE**=diabetes support education; **HbA_{1c}** = glycated hemoglobin; **NB**=naltrexone sustained-release (SR)/bupropion SR; **RCT** randomized controlled study; **QD**=once daily; **QOL**=quality of life

*Only outcomes relevant to this report have been included

Appendix 3: Summary of Critical Appraisal of Included Studies

First Author, Publication year	Strengths	Limitations
The Look AHEAD Research Group, [12] 2010	1. Large sample size (n=5145) provided sufficient power to detect clinically relevant differences between effects of study arms. 2. The study has a longer duration than many others and provides a more comprehensive long-term assessment of behavioral intervention on weight loss and associated health benefits. 3. Over 93% of participants were assessed at each year for the four years making it possible to evaluate more comprehensively the durability of measured outcomes and the long-term effects of the intervention.	The results may not be generalizable to all patients in a primary care facility for the following reasons 1. The study excluded patients younger than 45 years and older than 76 years old. In fact, 45% of prescreened participants (n=26522) were excluded and the major reason for exclusion was age (13.5%) 2. Only participants who could successfully complete a maximal graded exercise test at screening were included 3. Patients in the ILI group received free partial meal replacement which may not be offered in a primary care setting and may take away from the motivation of patients to rightly follow dietary recommendations.
O'Neil,[7] 2012	1. Demographic and clinical characteristic were well balanced across treatment arms at baseline. 2. Majority (90.5%) of the patients met the criteria for obesity (BMI≥30 kg/m^2) in addition to having Typr2 DM 3. Primary outcome endpoints were at levels of clinical significance. 4. Other clinical conditions associated with type 2 DM and obesity were assessed. 5. Robust reporting and statistical analysis.	1. Details of method of randomization is not provided; 2. Inclusion criteria required patients be taking metformin, SFU or both; and exclusion criteria included conditions which are common to obese type 2 DM patients. Therefor it is uncertain whether the study findings are generalizable to a broader diabetic population encountered in the primary care setting. 3. The study settings, academic and private research sites, differ considerably from primary setting in terms of staff and medical equipment. The impact of this on the results and the difference that could arise in a primary care setting is not known. 4. A large proportion (69%) of patient failed the screening process, which goes to question generalizability. 5. There was a high rate of premature discontinuation. However, the investigators report that attrition in pharmacological weight loss trials is generally high (36%) and analysis using both traditional LOCF approach and the completer population provided similar overall conclusions about the efficacy of lorcaserin.
Unick,[15] 2011	Large sample size and long duration of study;	1. Only severely obese patients 45 years of older were considered making the generalizability of the findings to other populations uncertain. 2. Participant received significant free meal replacement which may not be available from primary care settings. 3. Meal replacements, medication usage, and physical activity were self-reported and the extent of reliability is unknown. 4. Severely obese individuals participated in group sessions along with those with lesser degrees of obesity, which may have psychological implications for their level of motivation. Thus it is unclear how severely obese individual treated in primary care setting would respond outside a mixed group sessions.

First Author, Publication year	Strengths	Limitations
Davis,[4] 2012 USA	1. Used diabetic specific assessment tool validated among patients with type 1 and type 2 diabetes. 2. Used robust statistical analysis and reporting. 3. A high study retention rate at 12 months (81%)	1. This is a single setting (an academic medical center and University Hospital) study and generalizability of results to similar patients in primary care setting is uncertain. 2. Exclusion criteria included kidney or heart disease which are common among obese typ-2 DM patients and thus makes the external validity of the findings unclear. 3. Approximately half of the study population did not complete the Diabetes-39 question.
Luley,[8] 2011	1. Robust reporting to allow foster reproducibility. 2. Study was powered to provide at least 80% power to detect difference of 8kg body weight.	1. Six months is a relative short period for weight loss studies and it is unknown whether the gains could be sustained beyond that. Many longer duration studies report some losses in initial gains as the study progressed, and rate of weight loss also decreases with improved BMI. 2. Technology involved in the study may not be readily available in primary care settings, though investigators provided implementation cost analysis suggesting that it was comparable to other treatment options available in Germany where the study was conducted.
Hollander,[3] 2013	1. Double-blind randomized controlled study with relatively large sample size. 2. Robust reporting and statistical analysis including calculation of sample size to provide adequate power, and control for multiple comparisons. 3. Analyses were performed using both the modified intent-to-treat and the completer populations with provision for missing data imputation	1. Patients were excluded if they were receiving insulin therapy (which can promote weight gain) or glucagon-like peptide-1 receptor agonist therapy (which is associated with mild weight loss). Other exclusion criteria included HbA1c greater than 10% at screening were exclude. Therefore, screening failure was very (69%) suggesting study finding may not be applicable to many obese type 2 diabetes patients. 2. A active drug (NB) was compared with placebo which is not a feasible clinical choice of intervention for the targeted population. 3. Researchers received funding from Orexigen Therapeutics, Inc. the manufacturer of NB. In addition, the research team included employees and shareholders of Orixigen Inc. including consultants and member of the company's Advisory Board who participated in the study design, data interpretation and writing and reviewing of the manuscript, and approved the final version of the manuscript.

BMI=body-mass index; ; **BID**=twice daily; **DB**=double-blind; **DM**=diabetes mellitus; **DSE**=diabetes support education; **HbA1c** = glycated hemoglobin; **ILI**=intensive lifestyle intervention; **NB**=naltrexone sustained-release (SR)/bupropion SR; **RCT** randomized controlled study; **QD**=once daily; **QOL**=quality of life.

Appendix 4: Main Study Findings and Authors' Conclusions

First Author, Publication year	Main Study Findings*	Authors' Conclusions
The Look AHEAD Research Group,[12] 2010	1. Significantly greater weight losses occurred in the ILI group with average weight loss over 4 years of 6.15% (range: 6.39, 5.91) compared with 0.88% (range: 1.12, 0.64) in the DSE group (p<0.0001). 2. Significantly greater reductions in HbA1c occurred in the ILI group than DSE at each of the 4 years (p-values <0.0001 at all timepoints) with the greatest differences occurring at year 1. 3. Participants in ILL achieved significantly greater average increases in fitness over 4 years 12.73% (range: 11.87, 13.62) compared with DSE 1.96% (range: 1.07, 2.85), (p<0.0001). 4. Among participants using diabetes medications at baseline, more patients remained on these medications in DSE group than in ILI. 5. Differences in improvements between the two groups were generally greatest initially (first year) and decreased over time for several measure.	``This study shows that lifestyle interventions can produce long term weight loss and improvement in fitness and sustained beneficial effects on CVD risk factors.``[12] page 1569
O'Neil et al.[7] 2012	1. For patients using lorcaserin 44.7% of those who took 10 mg QD, and 37.5% of those who 10 mg BID lost at least 5% body weight compared with 16.1% of patients on placebo (P < 0.001), while 16.3, 18.1, and 4.4%, lost at least 10% of baseline body weight, respectively; (P < 0.001) 2. The proportion of patients who achieved HbA1c ≤7% at week 52 was significantly greater in the lorcaserin BID group (50.4%) and in the lorcaserin QD group (52.2%) than in the placebo group (26.3%).	"In summary, lorcaserin use for up to 1 year in obese and overweight patients with type 2 diabetes was associated with statistically significant and clinically meaningful weight reduction. Because significant improvements in glycemic control were also observed, lorcaserin could represent a useful weight management tool for overweight and obese type 2 diabetic patients in the future" [7] page 10
Unick,[15] 2011	1. Severely obese patients who used the ILI program achieved significantly greater average reduction in body weight compared to in overweight patients (9.04% versus -7.43%; p< 0.05) 2. Sixty-seven percent of severely obese individuals using the ILI achieved a ≥5% weight loss at 1 year with over 39% achieving a ≥10% weight loss at 1 year. 3. The proportion of severely obese participants who achieved HbA_{1C} <7% was significantly greater at 1 year	"These promising findings suggest that severely obese individuals with type 2 diabetes can be successfully treated through behavioral weight loss programs."[15] page 2155 "Based on the current findings, behavioral therapy should be considered a viable treatment option for this population."[15] page 2156

First Author, Publication year	Main Study Findings*	Authors' Conclusions
	than at baseline (71.3% versus 45.0%, respectively; P <0.05) with a 9% improvement in fasting glucose. 4. Seventeen percent of severely obese participants using insulin at baseline were no longer using insulin after 1 year of treatment. 5. Weight loss and glycemic control gains made by severely obese were similar to gains by those with lesser degrees of obesity.	
Davis,[4] 2012	1. Participants achieved a mean (±SD) weight loss at 12 months of 11 (±11) pounds, which did not differ significantly between dietary arms (P = 0.58). 2. Significant improvement (p=0.01) in QOL over baseline values occurred in the sexual function, and energy and mobility domains, and there was a trend toward improvement in anxiety and worry (P = .06). Difference between the dietary arms was not statistically significant (p=0.74). 3. Weight change and change in glycemic control (as determined by HbA_{1C}) were not correlated with the reported changes in QOL.	Obese patients with type 2 diabetes have various options for weight loss. A low-carbohydrate or low-fat diet achieved benefits in the diabetes-specific QOL scales of sexual function, energy and mobility, and a trend toward improvement in anxiety and worry. Low-carbohydrate and low-fat diets in this study did not appear to have differential effects on diabetes-specific quality of life measures.
Luley,[8] 2011	1. Patients in the ABC program achieved significantly greater mean weight loss compared with those in the control group. BMI reduced by 11.3% (± 5.9%) in the ABC group compared with 0.2% (± 2.9%) in the control group (p=0.000) 2. Significant weight reductions were achieved when energy expenditure had been increased from between 300 and 500 kcal/day at baseline to 1000 kcal/day and beyond. 3. Patients in the ABC group experienced improvements in glycemic control with a mean reduction in HbA1C of 10% (±5.9%) from baseline, while the control group had worsening glycemic control with increased HbA1c of 3% from baseline(p = 0.053). 4. The proportion of patients with HbA1c values above 7% decreased from 57% t at baseline to 26% at 6 months in the ABC group while the proportion increased from 74 t0 80% in the control group. 5. In the majority, drug treatment adjustments were	"The ABC program combines innovative telemonitoring with additional sensible measures. In obese diabetic patients it leads not only to a pronounced weight loss but also to relevant metabolic improvements and reductions in antidiabetic drug use."[8] page 293

First Author, Publication year	Main Study Findings*	Authors' Conclusions
	necessary during the first months of the ABC program indicating that the changes in diet combined with the increased exercise-related energy consumption lead to an early improvement of carbohydrate metabolism.	
Hollander,[3] 2013	1. NB resulted in significantly greater weight reduction than placebo (25.0 vs. 21.8%; P<0.001) 2. Proportion of patients achieving ≥5% weight loss was significantly greater with NB than placebo (44.5 vs. 18.9%, P <0.001) 3. More patients treated with NB than placebo achieved ≥5 and ≥10% reduction in body weight at week 56 (al P <0.001 in both cases) 4. Significantly greater HbA1c reduction occurred in the NB group than placebo (20.6 vs. 20.1% P <0.001), 5. Percent of patients achieving HbA1c <7% was significantly greater with NB than with placebo (44.1 vs. 26.3%; P <0.001) 6. HbA1c change was significantly correlated with change in body weight with both treatment arms (NB mITT: r = 0.509, P <0.001; placebo: r = 0.168, P <0.05). 7. Over the course of the study, fewer NB-treated patients required an increase in dose or the addition of another oral antidiabetic drug (22.3% NB vs. 35.2% placebo; P <0.01).	"NB therapy in overweight/obese patients with type 2 diabetes induced eight loss, which was associated with improvements in glycemic control and select cardiovascular risk factors and was generally well tolerated with a safety profile similar to that in patients without diabetes."[3] page 4022

BMI=body-mass index; ; **BID**=twice daily; **DB**=double-blind; **DM**=diabetes mellitus; **DSE**=diabetes support education; **HbA1c**=glycated hemoglobin; **ILI**=Intensive lifestyle intervention; **NB**=naltrexone sustained-release (SR)/bupropion SR; **RCT** randomized controlled study; **QD**=once daily; **QOL**=quality of life; **SD**=standard deviation

*Only finding relevant to this report (i.e. changes in weight, BMI, and glycemic control) have been presented

Appendix 5: Secondary Analyses of Data from the Look AHEAD Trial- Objectives, Main Findings and Authors' Conclusions

First Author, Publication year	Objectives	Main Study Findings*	Authors' Conclusions
Espeland,[13] 2013	To compare the effects of 4 years of ILI on weight, fitness, and cardiovascular disease risk factors in older and younger individuals.	1. Patients in the ILL group achieved significantly better outcomes than those in the DSE group regardless of whether they were younger[a] or older[b]. (see main finding for the Look AHEAD trial in Appendix 4) 2. Intervention-related mean weight losses were greater in older than younger participants (6.2% versus5.1%; interaction p=0.006). 3. Older and younger participants achieved comparable relative mean increase in fitness with mean differences of 0.56 METs* (95% CI: 0.41, 0.71) versus 0.53 METs* (95% CI: 0.45, 0.61; interaction p=0.72). 4. The ILL produced mean decrease in HbA1c of 0.21% over baseline (p<0.001)	``Intensive lifestyle intervention targeting weight loss and increased physical activity is effective in overweight and obese individuals to produce sustained weight loss and improvements in fitness and cardiovascular risk factors.``[13] page 912
Faulconbridge,[14] 2012	To determine whether moderate weight loss would be associated with incident symptoms of depression and suicidal ideation, and whether symptoms of depression at baseline would limit weight loss at 1 year.	1. Participants in ILI had a reduction of 1.4 ± 4.7 points on the BDI[c], compared to 0.4 ± 4.5 for DSE (P < 0.001, effect size = 0.23). 2. At 1 year, the incidence of potentially significant symptoms of depression was significantly lower in the ILI than DSE group (6.3% vs. 9.6%) (Relative Risk (RR) = 0.66, 95% CI: 0.5, 0.8; P < 0.001). 3. Participants in the ILL group with symptoms of depression at baseline achieved a comparable mean (±SD) weight loss as those without symptoms of depression (7.8% (± 6.7%) compared with 8.7% (± 6.9%), without a clinically meaningful difference between the two.	"The present findings suggest that overweight and obese individuals with mild or greater symptoms of depression can successfully participate in a behavioral weight loss program and should be encouraged to do so."[14] page 790
Rejeski,[1] 2012	1. To examined the decline in self-reported limitations in mobility[d] during the first 4 years of the Look AHEAD study; 2. To evaluated how the decline in mobility was influenced by the intervention; and 3. To evaluate whether observed differences were mediated by weight	1. The ILI group had a relative reduction of 48% in the risk of loss of mobility compared with the DSE group (OR= 0.52; 95% CI: 0.4, 0.63; P<0.001). 2. Both weight loss and improved fitness were significant mediators of the reduction in the mobility-related disability (P<0.001 for both	"Weight loss and improved fitness slowed the decline in mobility in overweight adults with type 2 diabetes."[1] page 1209

First Author, Publication year	Objectives	Main Study Findings*	Authors' Conclusions
	loss or an improvement in fitness.	variables). 3. For every relative reduction of 1% in weight and relative improvement of 1 % in fitness, there was a 7.3% and 1.4% reduction, respectively, in the risk of loss of mobility.	
Unick,[15] 2011	To examined the effect of ILI on weight loss, CVD risk, and program adherence in participants with type 2 diabetes who were severely obese compared with overweight (BMI 25 to <30 kg/m^2), class I obese (BMI 30 to <35 kg/m^2), and class II obese (BMI 35 to <40 kg/m^2) participants at year 1 of the Look AHEAD trial.	1. Severely obese patients who used the ILI program achieved significantly greater average reduction in body weight compared with overweight patients (9.04% versus -7.43%; p< 0.05). 2. Weight loss in the severely obese patients was comparable to that in class obese I (-8.72 ± 6.4%) and class II obese (-8.64 ±7.4%) patients. 3. Sixty-seven percent of severely obese individuals using the ILI achieved a ≥5% weight loss at 1 year with over 39% achieving a ≥10% weight loss at 1 year. 4. The proportion of severely obese participants who achieved HbA_{1C} <7% was significantly greater at 1 year than at baseline (71.3% versus 45.0%, respectively; P <0.05) with a 9% improvement in fasting glucose. 5. Seventeen percent of severely obese participants using insulin at baseline were no longer using insulin after 1 year of treatment. 6. Adherence did not differ among weight categories in the ILI treatment group.	"These promising findings suggest that severely obese individuals with type 2 diabetes can be successfully treated through behavioral weight loss programs."[15] page 2155 "Based on the current findings, behavioral therapy should be considered a viable treatment option for this population."[15] page 2156
Wadden,[16] 2001 USA	To further describe the 4-year weight losses in the ILI and DSE groups of the Look AHEAD trial and, to identify participants' demographic characteristics and lifestyle behaviors that were associated with long-term weight loss within the ILI group.	1. Among participants who lost ≥10% at 1 year, those who maintained this loss at year 4 completed significantly more treatment contacts per year in years 2–4 than did individuals who regained to their baseline weight (N = 88) or who maintained a loss of only 0–4.9% (N = 174). 2. Similarly, the 10% maintainers reported significantly lower calorie intake and greater physical activity at year 4 than did	"These results provide critical evidence that a comprehensive lifestyle intervention can induce clinically significant weight loss (i.e., ≥5%) in overweight/obese participants with type 2 diabetes and maintain this loss in more than 45% of patients at 4 years."[16] page 1987 "We believe that the successful

First Author, Publication year	Objectives	Main Study Findings*	Authors' Conclusions
		participants in the three other weight categories. 3. The odds of achieving a loss ≥10% of initial weight at year 4 were 9.8 (95% CI: 6.99–13.74) times greater for participants who lost ≥10% at year 1 compared to participants who lost <5% at year 1 and 2.0 (95% CI: 1.41–2.96) times greater for participants who had lost 5.0–9.9% at year 1 compared with those who lost <5% at year 1. 4. Similar analyses revealed that the odds of achieving a loss ≥5% at year 4 were 9.3 (95% CI: 7.27–11.83) times greater for participants who lost ≥10% at 1 year and 2.4 (95% CI: 1.88–3.04) times higher for individuals who lost 5.0–9.9%, compared to participants who lost <5% the first year.	maintenance of weight loss in ILI participants was attributable to their being provided twice-monthly counseling contacts with their lifestyle interventionist to facilitate continued adherence to the study's diet and activity goals."[16] page 1994

BMI=body-mass index; BDI=Beck depression inventory; **BID**=twice daily; **DB**=double-blind; **DM**=diabetes mellitus; **DSE**=diabetes support education; **HbA1c**=glycated hemoglobin; **ILI**=Intensive lifestyle intervention; **MET**=metabolic-equivalent; **NB**=naltrexone sustained-release (SR)/bupropion SR; **RCT** randomized controlled study; **QD**=once daily; **QOL**=quality of life; **SD**=standard deviation

*MET is defined as the amount of energy expended at resting. Peak MET capacity was estimated, using standardized equations, from performance on a graded exercise treadmill test administered at baseline, year 1 and year 4, and was the measure of fitness.

[a] For this analysis, younger refers to participants aged 45 to 64 years

[b] For this analysis, older refer to participants aged 65 to 76 years

[c] Potentially significant symptoms of depression were defined by a BDI score ≥10.

[d] Mobility was assessed on the basis of 6 of 11 items on the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) Physical Functioning subscale.